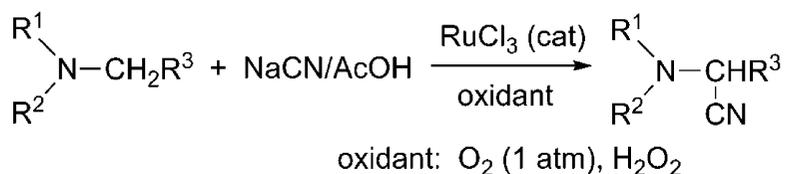Article

Ruthenium-Catalyzed Oxidative Cyanation of Tertiary Amines with Molecular Oxygen or Hydrogen Peroxide and Sodium Cyanide: sp C#H Bond Activation and Carbon#Carbon Bond Formation

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Ruthenium-Catalyzed Oxidative Cyanation of Tertiary Amines with Molecular Oxygen or Hydrogen Peroxide and Sodium Cyanide: sp³ C−H Bond Activation and Carbon−Carbon Bond Formation

Shun-Ichi Murahashi,*,†,‡ Takahiro Nakae,† Hiroyuki Terai,† and Naruyoshi Komiya†

Department of Chemistry, Graduate School of Engineering Science, Osaka University, 1-3 Machikaneyama, Toyonaka, Osaka 560-8531, Japan, and Department of Applied Chemistry, Faculty of Engineering, Okayama University of Science, 1-1 Ridaicho, Okayama, Okayama 700-0005, Japan

Received March 8, 2008; E-mail: murahashi@high.ous.ac.jp

Abstract: Ruthenium-catalyzed oxidative cyanation of tertiary amines with molecular oxygen in the presence of sodium cyanide and acetic acid gives the corresponding α-aminonitriles, which are highly useful intermediates for organic synthesis. The reaction is the first demonstration of direct sp³ C−H bond activation α to nitrogen followed by carbon−carbon bond formation under aerobic oxidation conditions. The catalytic oxidation seems to proceed by (i) α-C−H activation of tertiary amines by the ruthenium catalyst to give an iminium ion/ruthenium hydride intermediate, (ii) reaction with molecular oxygen to give an iminium ion/ruthenium hydroperoxide, (iii) reaction with HCN to give the α-aminonitrile product, H_2O_2, and Ru species, (iv) generation of oxoruthenium species from the reaction of Ru species with H_2O_2, and (v) reaction of oxoruthenium species with tertiary amines to give α-aminonitriles. On the basis of the last two pathways, a new type of ruthenium-catalyzed oxidative cyanation of tertiary amines with H_2O_2 to give α-aminonitriles was established. The α-aminonitriles thus obtained can be readily converted to α-amino acids, diamines, and various nitrogen-containing heterocyclic compounds.

Introduction

Catalytic functionalization of amines by direct C−H activation has attracted much interest in organic chemistry and the fine chemical industry in recent years, since functionalized amines are versatile intermediates and have been widely used in the construction of biologically active compounds and functional materials. Direct introduction of a substituent at the α position of tertiary amines would be performed by α-C−H activation and subsequent carbon−carbon bond formation. In order to activate sp³ C−H bonds of tertiary amines, one can use two strategies: (i) C−H activation upon treatment with oxometal (M=O) species such as cytochrome P-450 enzyme (Scheme 1a)[1,2] and (ii) C−H activation with low-valence metal catalysts at the α position of amines (Scheme 1b).[3] In either case, generation of iminium ion intermediates followed by reactions with carbon pronucleophiles would give α-substituted products, as shown in Scheme 1.

Scheme 1. Substitution at the α Position of Tertiary Amines by (a) C−H Activation with M=O Species and (b) C−H Activation with Low-Valence Metal Complexes
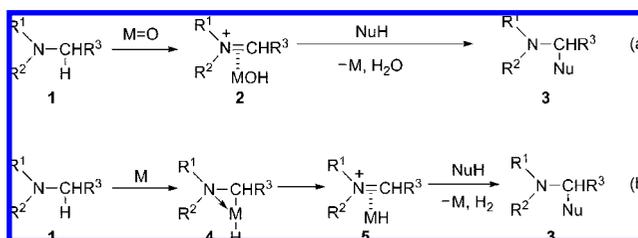

The former strategy is oxidative activation of α-C−H bonds of tertiary amines. In order to generate reactive species for selective oxidation, much effort has been devoted to simulation of the functions of cytochrome P-450.[1,2] One of the typical functions of cytochrome P-450 is chemoselective demethylation of *N*-methyl tertiary amines. In 1988, we found that ruthenium-catalyzed oxidation of tertiary amines with *t*-BuOOH gives α-*tert*-butyldioxyamines (**6a**),[4] as shown in Scheme 2.

† Osaka University.
‡ Okayama University of Science.
(1) (a) *Cytochrome P-450, Structure, Mechanism, and Biochemistry*, 2nd ed.; Ortiz de Montellano, P. R., Ed.; Plenum Press: New York, 1995. (b) Gorrod, J. W. *Biological Oxidation of Nitrogen*; Elsevier/North Holland Biomedical Press: New York, 1978.
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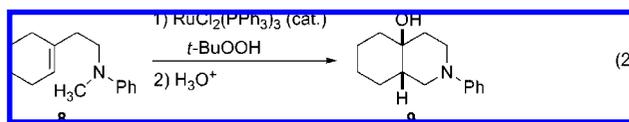
(3) (a) Murahashi, S.-I.; Takaya, H. *Acc. Chem. Res.* **2000**, *33*, 225−233. (b) Murahashi, S.-I.; Naota, T. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1805−1824. (c) *Handbook of C−H Transformations: Applications in Organic Synthesis*; Dyker, G., Ed.; Wiley-VCH: Weinheim, Germany, 2005. (d) Campos, K. R. *Chem. Soc. Rev.* **2007**, *36*, 1069−1084. (e) Godula, K.; Sames, D. *Science* **2006**, *312*, 67−72. (f) Tobisu, M.; Chatani, N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1683−1684.
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Scheme 2. Two-Step Oxidative Functionalization of a C−H Bond in Tertiary Amines

a: R = t-Bu, R' = t-BuO
b: R = H, R' = Me
c: R = MeCO, R' = Ac
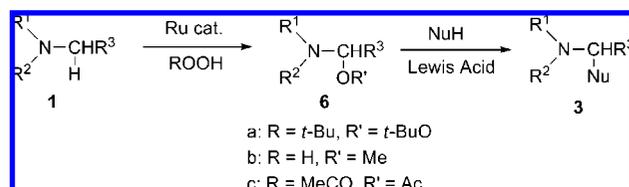
The products **6a** can be converted into the corresponding secondary amines upon hydrolysis similar to enzyme reactions.[1] This cytochrome P-450-type oxidation reaction can be applied to various substrates. Thus, ruthenium-catalyzed oxidations of tertiary amines[4,5] and amides[6] with peroxides give the corresponding α-oxygenated products highly efficiently, while oxidative transformation of secondary amines gives imines.[7] Strained and unstable of azetidinone molecules can be oxidized selectively. Thus, ruthenium-catalyzed oxidation of β-lactams with peracetic acid in acetic acid gives 4-acetoxy-2-azetidinones.[6] By means of an industrial process, 100 tons per year of **7** is now being produced as a versatile intermediate for synthesis of fourth-generation antibiotics (eq 1).
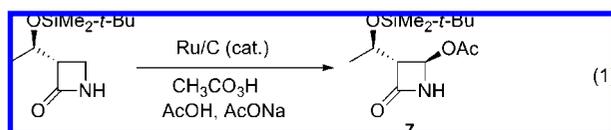
The α-oxygenated products **6** are useful synthetic intermediates because they can be easily transformed into the corresponding α-functionalized compounds **3** by reaction with various carbon nucleophiles (Scheme 2).[8] Typically, the reaction of α-*tert*-butyldioxyamines **6a** with allyltrimethylsilane gives α-allylated amines.[8a] Interestingly, an intramolecular version of the carbon−carbon bond formation can be applied to the synthesis of cyclic compounds via olefin−iminium ion cyclization. Typically, *N*-methyl-*N*-2-(1-cyclohexenyl)ethylaniline (**8**) can be converted into *cis*-α-hydroxy-2-phenyldecahydroisoquinoline (**9**) by ruthenium-catalyzed oxidation followed by treatment with an aqueous CF₃CO₂H solution (eq 2): Furthermore, stereose-

lective biomimetic construction of the piperidine skeleton **11** from *N*-methylhomoallylamine (**10**) has been achieved (eq 3):[4]
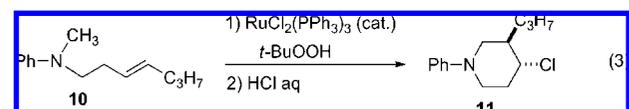
The second strategy for α-C−H activation adjacent to nitrogen can be achieved upon treatment with low-valence transition-metal complexes, as depicted in Scheme 1b. In 1978, on the basis of our findings on transition-metal-catalyzed alkyl-

group exchange reactions and hydrolysis reactions of tertiary amines, we concluded that activation of an sp³ C−H bond of a tertiary amine by low-valence transition-metal catalysts generally occurs, giving an iminium ion−metal complex (**5**).[2b,9] This is in contrast to activation of a primary or secondary amine, which gives an imine−metal complex.[10,11] As shown in Scheme 1b, coordination of the nitrogen to the metal and overlap of the metal orbital with the α-C−H bond would induce C−H activation to form the η²-iminium hydride metal complex **5**. This has been proved by racemization experiments at the chiral α carbon of tertiary amines and deuterium-labeling experiments at the α and β positions.[9] Isolation of the Pd−iminium ion complex and determination of its structure by X-ray diffraction have been performed elegantly by Lu and Peters.[12] Similar C−H activation in ruthenium cluster-catalyzed alkyl-exchange reactions has been demonstrated by Wilson and Laine.[13] This C−H activation is the key step in the asymmetric isomerization of allylamines to enamines in the industrially important chiral menthol synthesis.[14]

Other attractive metal-catalyzed C−H activations of tertiary amines have been reported. Murai, Chatani et al.[15] demonstrated that tertiary amines bearing an *N*-2-pyridyl group undergo α-C−H activation adjacent to nitrogen and subsequent carbonylation or coupling with an olefin by a pendant directing group to chelate the metal catalyst. Sames and co-workers[16] reported the elegant iridium-catalyzed formation of pyrrolizidinones from *N*-acylated pyrrolidines, which relied on direct α-C−H insertion followed by intramolecular C−C bond formation with an olefin tether. Insertion of carbenoids into C−H bonds adjacent to nitrogens of tertiary amines has been found to proceed selectively.[17]
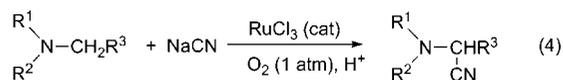
In a search for an environmentally benign and effective method for direct oxidative transformation of amines, we aimed

(7) (a) Murahashi, S.-I.; Naota, T.; Taki, H. *J. Chem. Soc., Chem. Commun.* **1985**, 613–614. (b) Murahashi, S.-I.; Okano, Y.; Sato, H.; Nakae, T.; Komiya, N. *Synlett* **2007**, 1675–1678. (c) Murahashi, S.-I.; Shiota, T. *Tetrahedron Lett.* **1987**, *28*, 2383–2386. (d) Murahashi, S.-I.; Mitsui, H.; Shiota, T.; Tsuda, T.; Watanabe, S. *J. Org. Chem.* **1990**, *55*, 1736–1744. (e) Mitsui, H.; Zenki, S.; Shiota, T.; Murahashi, S.-I. *J. Chem. Soc., Chem. Commun.* **1984**, 874–875.
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(12) A Pd−iminium ion complex was isolated, and its structure was determined by X-ray diffraction studies. See: Lu, C. C.; Peters, J. C. *J. Am. Chem. Soc.* **2004**, *126*, 15818–15832.
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(5) Murahashi, S.-I.; Naota, T.; Miyaguchi, N.; Nakato, T. *Tetrahedron Lett.* **1992**, *33*, 6991–6994.
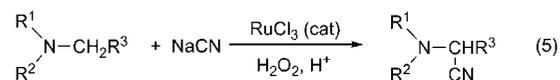(6) (a) Murahashi, S.-I.; Naota, T.; Kuwabara, T.; Saito, T.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1990**, *112*, 7820–7822. (b) Murahashi, S.-I.; Saito, T.; Naota, T.; Kumobayashi, H.; Akutagawa, S. *Tetrahedron Lett.* **1991**, *32*, 5991–5994.

at direct oxidative cyanation of tertiary amines by simultaneously accomplishing two challenging tasks: (1) oxidation with molecular oxygen, an environmentally benign oxidant, and (2) trapping of the iminium ion intermediates with a carbon nucleophile under oxidative conditions to give a carbon–carbon bond-formation product. Here we report that ruthenium-catalyzed oxidative cyanation of tertiary amines with molecular oxygen in the presence of sodium cyanide gives the corresponding α-aminonitriles highly efficiently (eq 4):[18]

$$R^1\underset{R^2}{\diagup}N-CH_2R^3 \ + \ NaCN \ \xrightarrow[\ O_2\ (1\ atm),\ H^+\ ]{RuCl_3\ (cat)} \ R^1\underset{R^2}{\diagup}N-\underset{CN}{\underset{|}{CH}}R^3 \qquad (4)$$

This is the first reported example of an aerobic catalytic method for carbon–carbon bond formation under oxidative conditions. The method is environmentally benign and highly useful for organic synthesis. The α-aminonitriles thus obtained exhibit valuable reactivities and are versatile intermediates for organic synthesis.[19] The nitrile functionality can be hydrolyzed readily to produce α-amino acids. Nucleophilic addition to the nitrile group provides valuable access to α-amino aldehydes, α-amino ketones, α-amino alcohols, and 1,2-diamines.[18b,19]

On the basis of a mechanistic investigation of the aerobic oxidative cyanation reaction, we found that similar oxidative cyanation occurs upon treatment with hydrogen peroxide. Thus, ruthenium-catalyzed oxidative cyanation of tertiary amines with hydrogen peroxide in the presence of sodium cyanide gives the corresponding α-aminonitriles highly efficiently (eq 5):[20]

$$R^1\underset{R^2}{\diagup}N-CH_2R^3 \ + \ NaCN \ \xrightarrow[\ H_2O_2,\ H^+\ ]{RuCl_3\ (cat)} \ R^1\underset{R^2}{\diagup}N-\underset{CN}{\underset{|}{CH}}R^3 \qquad (5)$$

Recently, Li and co-workers[21,22] reported interesting copper-catalyzed oxidative α-functionalizations of tertiary amines using *tert*-butyl hydroperoxide in the presence of carbon pronucleophiles. Thus, copper-catalyzed oxidation of tertiary amines with *t*-BuOOH in the presence of alkynes,[21a] indoles,[21b] nitromethane,[21c] and malonates[21d] gives the corresponding α-substituted amines. Doyle and co-workers[23] reported unique dirhodium-catalyzed oxidative carbon–carbon bond formation in tertiary amines upon treatment with *t*-BuOOH in the presence of siloxyfurans.

In this paper, full details regarding the scope and reaction mechanism of aerobic ruthenium-catalyzed oxidative cyanation of tertiary amines as well as of the similar oxidative cyanation reaction with H₂O₂ are described.

Results and Discussion

Ruthenium-Catalyzed Oxidative Cyanation of Tertiary Amines with Molecular Oxygen. On the basis of our previous findings that transition-metal-catalyzed alkyl-group exchange

(18) (a) Murahashi, S.-I.; Komiya, N.; Terai, H.; Nakae, T. *J. Am. Chem. Soc.* **2003**, *125*, 15312–15313. Introduced as a highlight; see: (b) North, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4126–4128.
(19) Enders, D.; Shilvock, J. P. *Chem. Soc. Rev.* **2000**, *29*, 359–373.
(20) Murahashi, S.-I.; Komiya, N.; Terai, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 6931–6933.
(21) (a) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 11810–11811. (b) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 6968–6969. (c) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 3672–3673. (d) Li, Z.; Li, C.-J. *Eur. J. Org. Chem.* **2005**, 3173–3176.
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(23) Catino, A. J.; Nichols, J. M.; Nettles, B. J.; Doyle, M. P. *J. Am. Chem. Soc.* **2006**, *128*, 5648–5649.

Table 1. Catalytic Activities for Oxidative Cyanation of **12** with Molecular Oxygen[a]

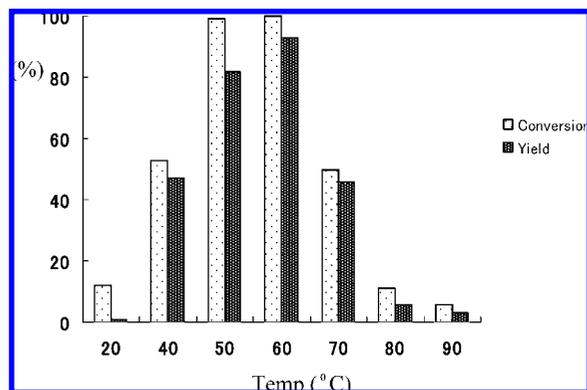| entry	catalyst	conversion (%)[b]	yield of **13** (%)[b]
1	RuCl₃	99	93
2	K₂[RuCl₅(H₂O)]	99	89
3	Ru₂(OAc)₄Cl	99	93
4	RuCl₂(PPh₃)₃	99	79
5	Ru(bpy)₂Cl₂	93	80
6	Pr₄NRuO₄	99	65
7	RuO₂	86	76
8	MnCl₂	44	40
9	CuCl₂	34	26

[a] A mixture of **12** (1.0 mmol), catalyst (0.05 mmol), NaCN (1.2 mmol), and CH₃CO₂H (6 mmol) in methanol (1.2 mL) was stirred under O₂ (1 atm) at 60 °C for 2 h. [b] Determined by GLC analysis using an internal standard.

Table 2. Effect of Solvents on Ruthenium-Catalyzed Oxidative Cyanation of **12** with Molecular Oxygen[a]

entry	solvent	time (h)	conversion (%)[b]	yield of **13** (%)[b]
1	CH₃OH	1	52	51
2	CH₃OH	2	99	93
3[c]	CH₃OH	1	<1	trace
4	CH₃CO₂H	1	42	34
5	C₂H₅OH	1	98	88
6	C₂H₅OH	2	99	88
7	i-PrOH	1	48	40
8	EtOAc	1	60	40
9	CH₃CN	1	24	16
10	H₂O	1	22	3

[a] A mixture of **12** (1.0 mmol), RuCl₃ (0.05 mmol), NaCN (1.2 mmol), and CH₃CO₂H (6 mmol) in solvent (1.2 mL) was stirred under O₂ (1 atm) at 60 °C for 2 h. [b] Determined by GLC analysis using an internal standard. [c] Reaction conducted in the absence of acetic acid.

and hydrolysis reactions of tertiary amines occur via α-C–H activation followed by formation of an iminium ion intermediate,[9] we attempted in vain to trap the iminium ion intermediate with a carbon nucleophile. However, we succeeded in trapping the intermediate under oxidative conditions. We examined catalytic aerobic oxidation of *N,N*-dimethylaniline (**12**) in the presence of sodium cyanide (eq 6): The activities of various
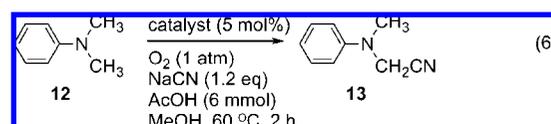
catalysts are summarized in Table 1. RuCl₃, K₂[RuCl₅(H₂O)], and Ru₂(CH₃CO₂)₄Cl (entries 1–3, respectively) proved to be excellent catalysts for aerobic oxidative cyanation, while RuCl₂(PPh₃)₃, Ru(bpy)₂Cl₂, Pr₄NRuO₄, and RuO₂ (entries 4–7, respectively) showed moderate catalytic activities. Ruthenium complex catalysts such as Ru₃O(OAc)₆(H₂O)₃, [Ru(CO)₃Cl₂]₂, 5% Ru/C, K₄Ru(CN)₆, and Ru(TPFPP)(CO)[24] and metal salt catalysts such as MnCl₂ (entry 8), CuCl₂ (entry 9), and FeCl₃ showed low catalytic activities.

The effect of the solvent was dramatic, as shown in Table 2. Methanol and ethanol were excellent solvents, but 2-propanol and ethyl acetate were not. Acetonitrile and water resulted in very low conversion. It is important to note that acetic acid is essential: no cyanation took place in the absence of acetic acid (entry 3), indicating that the reagent is HCN rather than CN⁻.

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Figure 1. Effect of temperature on RuCl$_3$-catalyzed oxidative cyanation with molecular oxygen. Conditions: **12** (1.0 mmol), RuCl$_3$ (0.05 mmol), NaCN (1.2 mmol), and CH$_3$CO$_2$H (6 mmol) in methanol (1.2 mL) stirred under O$_2$ (1 atm) for 2 h.

The reaction was found to be extremely sensitive to the reaction temperature. The effect of temperature on oxidative cyanation of **12** is shown in Figure 1. The product yield increased from 1 to 93% when the reaction temperature was raised from 20 to 60 °C. The maximum yield was obtained at 60 °C, above which the yield rapidly decreased with increasing reaction temperature.

Typical results for ruthenium-catalyzed aerobic oxidative cyanation of tertiary amines are summarized in Table 3. The reaction of **12** with sodium cyanide (1.2 equiv) in the presence of RuCl$_3$ catalyst and acetic acid in methanol under molecular oxygen (1 atm, balloon) at 60 °C for 2 h gave *N*-methyl-*N*-phenylaminoacetonitrile in 88% isolated yield [93% yield by gas−liquid chromatography (GLC)] (entry 1). The other products formed were *N*-methylaniline (<3% GLC yield) and *N*-methylformanilide (trace). The reaction can be applied to substituted *N,N*-dimethylanilines bearing either electron-donating or electron-withdrawing groups (entries 2−7). It is noteworthy that the present reaction tolerates other functional groups such as bromine (entry 7), which is reactive toward low-valence ruthenium species. The *N*-methyl group was oxidized chemoselectively in the presence of other alkyl groups. Thus, the reaction of *N*-ethyl-*N*-methylaniline (entry 8) gave *N*-ethyl-*N*-phenylaminoacetonitrile in 57% yield along with 2-(*N*-methyl-*N*-phenylamino)propionitrile (4%). This is due to a steric effect, similar to that observed in chemoselective *N*-methyl oxidation using cytochrome P-450. The oxidative cyanation of *N*-phenyl-1,2,3,4-tetrahydroisoquinoline (entry 9) took place selectively at the C1 position, affording the corresponding α-cyanated compound in 79% yield. The reaction is very simple and convenient and can be applied in a preparative-scale synthesis. Typically, the reaction of *N,N*-dimethyl-4-methylaniline (4.1 g, 30 mmol) with NaCN (36 mmol) in the presence of acetic acid in methanol at 60 °C gave *N*-methyl-*N*-(4-methylphenyl)acetonitrile in 90% isolated yield (4.3 g). Tertiary alkylamines such as tributylamine and *N*-methylpyrrolidine did not undergo reaction under the present reaction conditions.

The present reaction is very simple; however, the reaction mechanism is not so simple, and its elucidation is of great interest. In order to clarify the mechanism, the relative rates of oxidative cyanation of para-substituted *N,N*-dimethylanilines (*p*-XC$_6$H$_4$NMe$_2$, where X = MeO, Me, H, Br) with molecular oxygen in the presence of sodium cyanide were examined by ^{1}H NMR analysis of the corresponding cyanated products. The measured rates for the RuCl$_3$-catalyzed reaction were well-

**Table 3.** Aerobic Ruthenium-Catalyzed Oxidative Cyanation of Tertiary Amines with Sodium Cyanide[a]

entry	substrate	time	products	yield[b]
1		2 h		88% (93%)[c]
2		1 h		94% (97%)[c]
3		1.5 h		84%
4[e]		24 h		80%
5		2 h		81%
6		4 h		65%
7		2 h		88%
8		24 h		57%[c] / 7%[c]
9		4 h		76% (79%)[d]
10		24 h		23%[d]

[a] A mixture of tertiary amine (1.0 mmol), RuCl$_3$ (0.05 mmol), NaCN (1.2 mmol), and CH$_3$CO$_2$H (6 mmol) in methanol (1.2 mL) was stirred under O$_2$ (1 atm) at 60 °C. [b] Isolated yield, unless otherwise noted. [c] Determined by GLC analysis using an internal standard. [d] Determined by ^{1}H NMR analysis. [e] Ru(bpy)$_2$Cl$_2$ was used instead of RuCl$_3$.

correlated ($r^2 = 0.999$) with the substituent constant (σ) values of the Hammett linear free energy relationship[25] (Figure 2). The value of the Hammett reaction constant (ρ) for this catalyst was −3.35 (entry 1 in Table 4), which is larger than the value of −0.84 obtained for the RuCl$_2$(PPh$_3$)$_3$-catalyzed oxidation of the same amines with *t*-BuOOH to give α-*tert*-butyldioxyamines (entry 3).[4] The negative value of ρ indicates cationic intermediacy in the rate-determining step.

The intra- and intermolecular deuterium isotope effects (k_H/k_D) for the RuCl$_3$-catalyzed oxidative cyanation of *N,N*-dimethylanilines and their deuterated analogues were determined to be 2.40 and 2.62, respectively (entry 1 of Table 4). These observed isotope effects are larger than the corresponding ones observed for *N*-demethylation with cytochrome P-450 (1.6−3.1[26] and 1.0−1.1[27]) (entry 5), suggesting that cleavage

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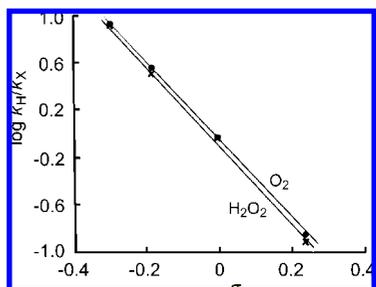
Figure 2. Hammett plots for RuCl$_3$-catalyzed oxidative cyanation of para-substituted *N,N*-dimethylanilines (*p*-XC$_6$H$_4$NMe$_2$ with X = MeO, Me, H, Br) with molecular oxygen (●) and hydrogen peroxide (×).

of the C—H bond proceeds via an intermediate bearing greater ionic character. The intramolecular deuterium isotope effects for the para-substituted *N*-methyl-*N*-trideuteromethylanilines *p*-X-C$_6$H$_4$NMeCD$_3$ (X = MeO, Me, H, Br) were dependent on the substituent σ values: the k_H/k_D values were 4.2, 3.1, 2.4, and 1.1, respectively. Thus, the values decreased on going from electron-donating to electron-withdrawing substituents, indicating that electron transfer from the amine to the ruthenium would take place in the initial step.[28]

The results of measurements of molecular oxygen uptake showed that 1 mol of molecular oxygen was consumed for every 2 mol of **12** oxidized under the standard reaction conditions, indicating that one molecule of molecular oxygen is used for the formation of two iminium ion intermediates, which are trapped with cyanide to give the corresponding α-aminonitrile.

The reaction can be rationalized in terms of the mechanism shown in Scheme 3. In this mechanism, the tertiary amine **1** coordinates to the low-valence ruthenium species Ru^n, yielding **14**. Electron transfer and subsequent hydrogen transfer from the amine to ruthenium results in the formation of an iminium ion/ruthenium hydride complex (**15**),[9] which undergoes reaction with molecular oxygen to form an iminium ion/Ru^{n}OOH complex (**16**). Such oxidation of a metal hydride (M—H) species with molecular oxygen to give a MOOH species[29,30] was demonstrated for the first time by asymmetric oxypalladation of allylphenols[29] and then by palladium-catalyzed aerobic oxidation of alcohols,[31] ruthenium-catalyzed aerobic oxidation

of alcohols,[32] and ruthenium-catalyzed oxidative transformation of primary amines to nitriles.[33] Subsequent reaction of the iminium ion/Ru^{n}OOH complex **16** with HCN, which is generated from NaCN and acetic acid under the reaction conditions,[34] gives the α-aminonitrile **19**, Ru^n, and H$_2$O$_2$. Reaction of Ru^n with the newly-formed H$_2$O$_2$ yields the Ru^{n+2}=O species **17**,[5,35] which reacts with another tertiary amine **1** to give the iminium ion intermediate **18** by electron transfer and subsequent hydrogen transfer.[4] The iminium ion intermediate **18** can be trapped with cyanide to afford **19**, Ru^n, and water, thereby completing the catalytic cycle. At the stage of the mechanism involving the transformation from **16** to **17**, an alternative direct pathway via protonolysis of **16** to give **17** cannot be excluded. It was confirmed that oxidative cyanation of tertiary amines with H$_2$O$_2$ to give α-aminonitriles occurred. The corresponding *N*-oxide of **12** could not be detected under the reaction conditions, although the RuCl$_3$-catalyzed aerobic oxidation of tertiary amines has been reported.[36] The mechanism involving oxidation with the *N*-oxide can thus be excluded. It is noteworthy that Baslé and Li[22] recently reported similar CuBr-catalyzed aerobic oxidative alkylation of isoquinolines with nitromethane.

Ruthenium-Catalyzed Oxidative Cyanation of Tertiary Amines with Hydrogen Peroxide. Given the reaction mechanism described above, we expected that ruthenium-catalyzed oxidative cyanation with H$_2$O$_2$ would occur, and indeed, RuCl$_3$-catalyzed oxidative cyanation of **12** with H$_2$O$_2$ in the presence of cyanide gave the corresponding α-cyanated amines highly efficiently. We examined the catalytic activities of various metal catalysts for the oxidative cyanation of **12** with H$_2$O$_2$ via eq 7, and
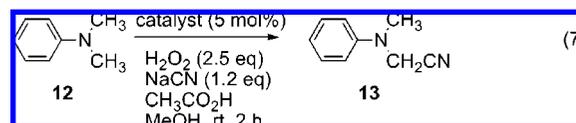
representative results are given in Table 5.

We found that the trend of catalytic activities for oxidation with H$_2$O$_2$ is similar to that described above for oxidation with molecular oxygen. As shown in Table 5, ruthenium complex catalysts showed high catalytic activities. Among them, RuCl$_3$ proved to be the best catalyst. Various solvents can be used for the present reaction. We found that methanol is the best solvent, although ethanol, ethyl acetate, acetonitrile, and dichloromethane can also be used. The addition of acetic acid was necessary for the reaction with sodium cyanide, and no reaction took place in the absence of acetic acid.

Representative results for oxidative cyanation of tertiary amines with H$_2$O$_2$ in the presence of sodium cyanide are provided in Table 6. Various tertiary amines can be converted into the corresponding α-aminonitriles highly efficiently. The reaction of substituted *N,N*-dimethylanilines bearing either

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Table 4. Kinetics and Isotope Effects of Catalytic Oxidative Cyanation of $XC_6H_4N(CH_3)_2$ to $XC_6H_4N(CH_3)CH_2Y$

entry	catalyst	oxidizing agent	Y	ρ	$k_H/k_D{}^a$	$k_H/k_D{}^b$	source
1	$RuCl_3$	O_2	CN	−3.35	2.40	2.62	this work
2	$RuCl_3$	H_2O_2	CN	−3.61	4.06	3.74	this work
3	$RuCl_2(PPh_3)_3$	t-BuOOH	OO-t-C_4H_9	−0.84	3.53	1.64	ref 4
4	$RuCl_3$	H_2O_2	OCH_3	−3.60	3.47	3.72	ref 5
5	cytochrome P-450	O_2	(OH)	−0.74	1.6−3.1	1.0−1.1	refs 26, 27

[a] Intramolecular deuterium isotope effect. [b] Intermolecular deuterium isotope effect.

Scheme 3. Proposed Mechanism for Ruthenium-Catalyzed Aerobic Oxidative Cyanation
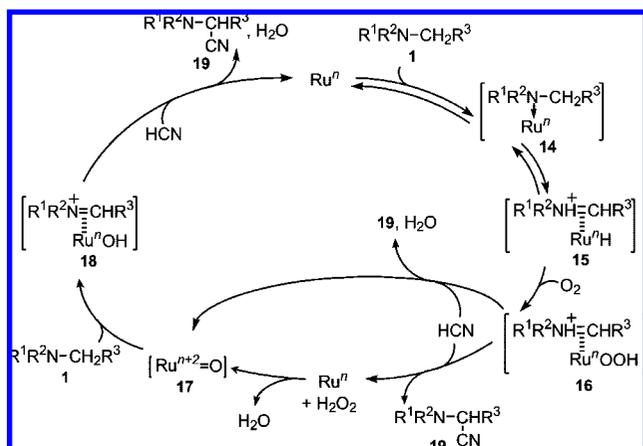
Table 5. Catalytic Activities for Oxidative Cyanation of **12** with 30% Hydrogen Peroxide in the Presence of Sodium Cyanide and Acetic Acid in Methanol

entry	catalyst	conversion (%)	yield of **13** (%)
1	$RuCl_3$	99	90
2	$RuCl_2(PPh_3)_3$	99	79
3	Pr_4NRuO_4	99	65
4	$MnCl_2$	48	41
5	$FeCl_3$	34	25

Table 6. Ruthenium-Catalyzed Oxidative Cyanation of Tertiary Amines with Hydrogen Peroxide[a]

[a] To a mixture of tertiary amine (1.0 mmol), $RuCl_3$ (0.05 mmol), NaCN (1.2 mmol), and CH_3CO_2H (6 mmol) in methanol (1.2 mL) was added dropwise a 30% H_2O_2 aqueous solution (2.5 mmol) over a period of 1 h. The mixture was stirred for the indicated time. [b] Determined by GLC analysis using an internal standard, unless otherwise indicated. [c] In this case, 1.5 mmol of H_2O_2 was used. [d] In this case, 1.0 mmol of H_2O_2 was used. [e] Determined by ^{1}H NMR analysis. [f] Isolated yield.

electron-donating or electron-withdrawing substituents gave the corresponding cyanated products (entries 2−4). Furthermore, the reaction can also be efficiently applied to cyclic amines. Thus, piperidine, pyrrolidine, and tetrahydroisoquinoline derivatives can be converted into the corresponding α-cyanoamines, respectively (entries 6−9). It is noteworthy that for cyanation of cyclic amines, the hydrogen peroxide system seems to be more efficient than the aerobic oxidation system (e.g., compare entry 8 with entry 10 of Table 3). This efficiency increase is due to the greater reactivity of the oxoruthenium species derived from hydrogen peroxide and low-valence ruthenium species in comparison with C−H activation followed by reaction with molecular oxygen in the aerobic oxidation system.

In order to clarify the mechanism, the relative reaction rates for oxidative cyanation of the four para-substituted *N,N*-dimethylanilines p-$XC_6H_4NMe_2$ (X = MeO, Me, H, Br) with H_2O_2 in the presence of sodium cyanide were determined by ^{1}H NMR analysis of the corresponding cyanated products. As before, the rate data were well-correlated ($r^2 = 0.998$) with the Hammett σ values, as shown in Figure 2. The ρ value was determined to be −3.61 (entry 2 in Table 4), which is close to the value of −3.60 obtained for the $RuCl_3$-catalyzed oxidation of p-substituted anilines with H_2O_2 in methanol to give α-methoxy compounds (entry 4),[5] suggesting the formation of cationic intermediacy in the rate-determining step. The intra- and intermolecular deuterium isotope effects k_H/k_D for the
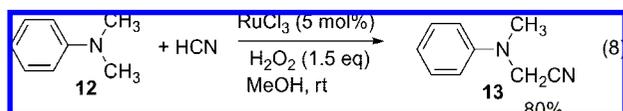
oxidative cyanation of *N,N*-dimethylanilines and their deuterated analogues were determined to be 4.06 and 3.74, respectively (entry 2). The observed intra- and intermolecular isotope effects are also similar to the corresponding ones (3.5 and 3.7) obtained for $RuCl_3$-catalyzed oxidation of para-substituted anilines with H_2O_2 in methanol (entry 4). However, they are larger than those observed for oxidative cyanation with O_2 as described above (2.40 and 2.62, respectively; entry 1), suggesting a more important contribution from C−H bond cleavage than from electron transfer in the rate-determining step.

Given these data, the present reaction can be rationalized in terms of the mechanism shown in Scheme 4. As we expected, this mechanism is consistent with a portion of the one shown in Scheme 3. The low-valence ruthenium species Ru^n reacts with H_2O_2 to give the oxoruthenium species Ru^{n+2}=O, which produces the iminium ion intermediate **18** by electron transfer

**Scheme 4.** Proposed Mechanism for Oxidative Cyanation with H$_2$O$_2$

Scheme 5. Usefulness of the α-Aminonitrile **13**
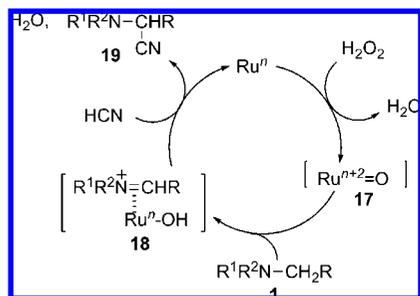
and subsequent hydrogen transfer.[37] Nucleophilic attack by hydrogen cyanide on the iminium ion intermediate gives the corresponding α-cyanated product, water, and the Ru^n species, completing the catalytic cycle.

The participation of hydrogen cyanide, which is formed from sodium cyanide and acetic acid under the reaction conditions, was confirmed by the following reactions. The ruthenium-catalyzed oxidation of **12** with H$_2$O$_2$ in the presence of hydrogen cyanide in methanol at room temperature (eq 8) gave the corresponding α-aminonitrile *N*-methyl-*N*-phenylaminoaceto-nitrile (**13**) in 80% yield: The similar reaction with *N*-
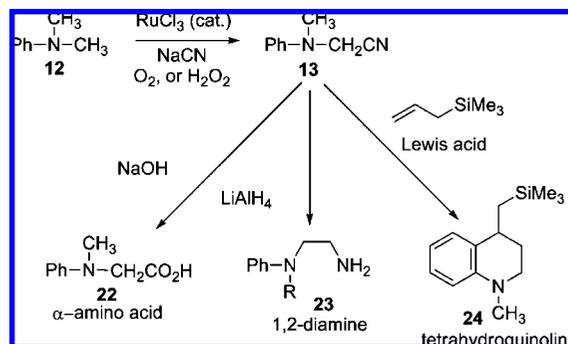

phenyltetrahydroisoquinoline (**20**) (eq 9) gave the corresponding α-cyanated tetrahydroisoquinoline **21** in 97% yield: However,
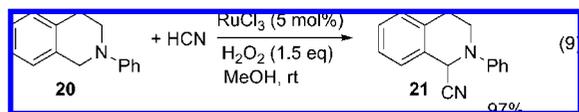
in the absence of hydrogen cyanide, the oxidation of **12** in MeOH gave α-methoxyamine in 82% isolated yield.[5] From this result, it could be inferred that the α-methoxyamine thus formed undergoes reaction with hydrogen cyanide under the reaction conditions to give the α-cyanated amine. However, this mechanism is unlikely because MeOH is not essential: other solvents, such as ethyl acetate and acetonitrile, can be used instead of MeOH for the oxidative cyanation.

One consequence of these catalytic cycles (Schemes 3 and 4) is that the steric center of the aminonitrile is created by the addition of cyanide to a ruthenium-coordinated iminium ion (complex **16** or **18**). Thus, by use of a chiral ligand attached to the ruthenium, it may be possible to develop a catalytic asymmetric synthesis of α-aminonitriles using this chemistry.

Transformation of α-Aminonitriles. The present ruthenium-catalyzed oxidative cyanation is very simple and highly useful for synthesis of α-aminonitriles.[18] It is comparable with Strecker reactions[38] but is superior to other methods, such as electrolysis of tertiary amines;[39] oxidation with chlorine dioxide,[40] 1-cyano-3-(1*H*)-1,2-benziodoxols,[41] singlet oxygen,[42] or mercuric acetate;[43] photoinduced reaction in the presence of tetracyanoet-

hylene;[44] and enzymatic reaction with rat liver microsomes.[45] Miura and co-workers[46] reported iron-catalyzed aerobic oxidative cyanation in the presence of benzoyl cyanide, giving the corresponding α-aminonitrile and formanilide in 63% and 25% yield, respectively.

The α-aminonitriles thus obtained are highly useful precursors for α-amino acids.[47] Thus, α-aminonitriles can be readily converted to *N*-aryl-α-amino acids. Typically, the alkaline hydrolyses of **13** and 2-cyano-*N*-(4′-methoxyphenyl)pyrrolidine gave *N*-methyl-*N*-phenylglycine (**22**) and *N*-(4′-methoxyphe-nyl)proline in 87% and 69% yield, respectively (Scheme 5). Furthermore, the α-aminonitriles can be converted into unsymmetrical 1,2-diamines, which are important ligands and precursors of biologically active compounds.[48] Typically, treatments of **13** and 1-cyano-*N*-(4′-methoxyphenyl)pyrrolidine with lithium aluminum hydride gave *N*-methyl-*N*-phenylethylenediamine (**23**) and 2-aminomethyl-*N*-(4′-methoxyphenyl)pyrrolidine in 92% and 99% yield, respectively. Furthermore, aminonitriles are versatile synthetic intermediates for the construction of quinoline skeletons. For example, the TiCl$_4$-promoted reaction of **13** with allyltrimethylsilane in CH$_2$Cl$_2$ gave 1-methyl-4-[(trimethylsi-

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lyl)methyl]-1,2,3,4-tetrahydroisoquinoline (**24**), an important precursor of quinoline alkaloids, in 75% isolated yield.

Conclusions

We have demonstrated novel ruthenium-catalyzed oxidative cyanation of tertiary amines upon treatment with molecular oxygen or hydrogen peroxide. The reactions proceed highly efficiently to give the corresponding α-cyanated amines, which are highly useful compounds for synthesis of various nitrogen compounds. The principle of direct sp^3 C−H bond activation α to nitrogen followed by carbon−carbon bond formation under oxidative conditions was first demonstrated. The biomimetic principle of this reaction will provide a powerful means for developing new types of catalytic aerobic oxidative transformation reactions.

Experimental Section

Caution! *All reactions and treatments must be carried out in a well-ventilated hood because highly toxic HCN is formed from NaCN in media that include acetic acid.*

General Procedure for Aerobic Ruthenium-Catalyzed Oxidative Cyanation of Tertiary Amines with Sodium Cyanide. Synthesis of *N*-Methyl-*N*-phenylacetonitrile (13). A 25 mL side-armed round-bottom flask equipped with a magnetic stirring bar was charged with RuCl$_3$ (13 mg, 5.0×10^{-2} mmol) and sodium cyanide (59 mg, 1.2 mmol). After the flask was filled with molecular oxygen (1 atm) with a balloon, methanol (1.2 mL), **12** (121 mg, 1.0 mmol), and acetic acid (360 mg, 6 mmol) were added. The mixture was stirred under the oxygen atmosphere at 60 °C. After 2 h, the mixture was poured into an aqueous NaHCO$_3$ solution and extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. The yields of *N*-methyl-*N*-phenylacetonitrile, *N*-methylaniline, and *N*-methylformamide were determined to be 93%, <3%, and trace, respectively, by GLC analyses using an internal standard of hexadecane. Chromatography on silica gel (hexane/ethyl acetate) gave pure **13** (130 mg, 88%) as a brown oil. IR (neat) ν (cm^{-1}): 3096, 2896, 2325 (C≡N), 1601, 1580, 1505, 1478, 1456, 1424, 1356, 1338, 1248, 1202, 1161, 1119, 1034, 999, 926, 870, 756, 693. ^{1}H NMR (CDCl$_3$, 270 MHz): δ 3.01 (s, 3H), 4.16 (s, 2H), 6.87 (dd, *J* = 8.7 and 1.1 Hz, 2H), 6.93 (dd, *J* = 6.5 and 0.86 Hz, 1H), 7.31 (ddd, *J* = 8.1, 8.1, and 1.1 Hz, 2H). ^{13}C-{^{1}H} NMR (CDCl$_3$, 68 MHz): δ 147.9, 129.5, 120.2, 115.4, 114.9, 42.3, 39.2. High-resolution electron-impact mass spectrometry: calcd for C$_9$H$_{10}$N$_2$, *m/z* 146.0844; found, *m/z* 146.0807.

Preparative Scale Reaction. Aerobic Ruthenium-Catalyzed Oxidative Cyanation of *N,N*-Dimethyl-4-methylaniline with Sodium Cyanide. A 200 mL side-armed round-bottom flask equipped with a magnetic stirring bar was charged with RuCl$_3$ (390 mg, 1.5 mmol) and sodium cyanide (1.77 g, 36.0 mmol). After the flask was filled with molecular oxygen (1 atm) with a balloon, methanol (36 mL), *N,N*-dimethyl-4-methylanline (4.05 g, 30.0 mmol), and acetic acid (10.8 g, 180 mmol) were added. The mixture was stirred under molecular oxygen at 60 °C. After 8 h, the mixture was poured into aqueous NaHCO$_3$ solution and extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. Removal of the solvent followed by washing of the residual solid with a small amount of hexane gave pure *N*-methyl-*N*-(4-methylphenyl)acetonitrile (4.31 g, 90%) as a pale brown solid.

General Procedure for Ruthenium-Catalyzed Oxidative Cyanation of Tertiary Amines with 30% Aqueous Hydrogen Peroxide in the Presence of Sodium Cyanide. Synthesis of 1-Cyano-2-phenyl-1,2,3,4-tetrahydrosioquinoline (21). A 25 mL side-armed round-bottom flask equipped with a magnetic stirring bar and a balloon filled with Ar was charged with RuCl$_3$ (13 mg, 5.0×10^{-2} mmol), sodium cyanide (59 mg, 1.2 mmol), 2-phenyl-1,2,3,4-tetrahydrosioquinoline (209 mg, 1.0 mmol), acetic acid (360 mg, 6 mmol), and MeOH (1.2 mL). To the mixture was added dropwise a 30% H$_2$O$_2$ aqueous solution (2.5 mmol) at room temperature over a period of 1 h, and the mixture was stirred for an additional 0.5 h. At the end of the reaction, the mixture was poured into an aqueous NaHCO$_3$ solution and extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. Chromatography on silica gel (hexane/ethyl acetate) gave 1-cyano-2-phenyl-1,2,3,4-tetrahydrosioquinoline (**21**) (164 mg, 70%) as a colorless solid. Mp: 101−102 °C. IR (KBr) ν (cm^{-1}): 3108, 2990, 2824, 2222 (C≡N), 1595, 1497, 1460, 1424, 1373, 1356, 1339, 1309, 1273, 1221, 1206, 1142, 1026, 995, 938, 889, 779, 745, 693, 613. ^{1}H NMR (CDCl$_3$, 270 MHz): δ 2.96 (dt, *J* = 16.1 and 3.7 Hz, 1H), 3.15 (ddd, *J* = 16.2, 10.5, and 5.9 Hz, 1H), 3.48 (ddd, *J* = 12.3, 10.5, and 4.3 Hz, 1H), 3.77 (ddd, *J* = 12.5, 6.1, 2.9, and 1.2 Hz, 1H), 5.50 (s, 1H), 7.01 (ddm, *J* = 7.3 and 2.2 Hz, 1H), 7.08 (ddm, *J* = 7.1 and 2.2 Hz, 2H), 7.19 (m, 6H). ^{13}C-{^{1}H} NMR (CDCl$_3$, 68 MHz): δ 148.4, 134.6, 129.7, 129.6, 129.3, 128.8, 127.1, 126.9, 121.9, 117.7, 117.6, 53.2, 44.2, 28.5. Anal. Calcd for C$_{16}$H$_{14}$N$_2$: C, 82.02; H, 6.02; N, 11.96. Found: C, 82.04; H, 6.05; N, 11.91.

Supporting Information Available: Detailed experimental procedures, including analytical and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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